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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,587	05/16/2001	Yoshiki Sasai	00766.000044.	1416

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
09/30/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/855,587	SASAI ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,15,18-21,23,24,72,74,75 and 80-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15,18-21,23,24,72,74,75 and 80-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 January 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 15, 18-21, 23-24, 72, 74-75, 80-87 are pending and under consideration. The amendment has been entered. Claims 2-14, 16-17, 22, 25-71, 73, 76-79 are canceled.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/10/09 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 15, 18-21, 23-24, 72, 74-75, 80-87 **stand** rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The present claims have been amended to recite and encompass a method that has culturing an embryonic stem cell in vitro in the absence of retinoic acid and in the presence of a stroma cell recognized by a monoclonal antibody produced by hybridoma FERM BP-7573 without forming embryoid body for a time period from 1 day to 14 days and then culturing continuously the cell in vitro in the absence of retinoic acid and in the presence of a stroma cell

recognized by a monoclonal antibody produced by hybridoma FREM BP-7573 without forming embryoid body. Literal support for these steps and what is accomplished by these steps cannot be found in the specification. Moreover, figurative support for these steps, wherein it results in "differentiation of an embryonic stem cell into a neural crest cell or a neural tube cell" cannot be found and appears to be inconsistent with the teachings of the present specification. More specifically, the culturing continuously the cell in vitro in the absence of retinoic acid and in the presence of a stroma cells without forming embryoid body is affecting the embryonic stem cell to differentiate into a neural crest cell or neural tube cell. The method steps in examples 1 or 14 of the specification, wherein EB5 embryonic stem cells cultured in the presence of stromal cells for 10 days exhibit neural cell specific markers so no support for culturing continuously as instantly claimed. It is noted that the Applicants fail to point to any specific support for the present claim amendments.

MPEP 2163.06 notes "If new subject matter is added to the disclosure, whether it be in the abstract, the specification, or the drawings, the examiner should object to the introduction of new matter under 35 U.S.C. 132 or 251 as appropriate, and require applicant to cancel the new matter. If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981). The examiner should still consider the subject matter added to the claim in making rejections based on prior art since the new matter rejection may be overcome by applicant. In an instance in which the claims have not been amended, per se, but the specification has been amended to add new matter, a rejection of the claims under 35 U.S.C. 112, first paragraph should be made whenever any of the claim limitations are affected by the added material. When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to

determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

To the extent that the claimed methods are not described in the instant disclosure, claims 1, 15, 18-21, 23-24, 72, 74-75, 80-87 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention since a disclosure cannot teach one to make or use something that has not been described.

The specification teaches the term "cell of neural tube" means a cell which constitutes a neural tube in the generation process of neural tube in the initial stage of development in chodrates [0192] and the term "cell of neural crest:" means a cell which constitutes a neural crest in the above generation process [0193]. However, applicants failed to provide guidance to correlate the induction of differentiation of embryonic stem cells into neural cell expressing neural surface markers into a neural crest cell or a neural tube cell that morphologically, physiologically or structurally meets the limitations of a neural tube or a neural crest cell. The mere expression of neural surface markers on the differentiated embryonic stem cells of the disclosed invention cannot support the morphological, structural and physiological limitations of these cells in the generation process of a neural crest or neural tube. **Mizuseki et al,** (PNAS, 100(10): 5828-5833, 2003) notes it remains to be known whether ES cell-derived neural precursors generated in vitro can produce the full dorsal-ventral range of neuroectodermal derivatives in response to embryonic positional information (p 5828, 1st column, 3rd paragraph). Further, the instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of producing the full dorsal-ventral range of

neuroectodermal derivatives in response embryonic positional information raised by the state of the art. Therefore, the skilled artisan would conclude that the state of art of producing neural crest cell or neural tube cell is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for producing these cells without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the specific steps for the production of a neural crest cells or neural tube cell with the structural, functional and morphological characteristics of said cells, the lack of direction or guidance provided by the specification to determine the specific steps for the production of a neural crest cells or neural tube cell, the absence of working examples that correlate the induction of differentiation of embryonic stem cells into neural cells expressing neural surface markers to the production of neural crest cells or neural tube cells, the unpredictable state of the art with respect to the production of a neural crest cells or neural tube cell, the undeveloped state of the art pertaining to the production of a neural crest cells or neural tube cell, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants argue in Example 1, antibodies against NCAM, against class IIIβ tublin2, against nestin3, against tyrosine hydroxylase4, against VAchT5, against GAD6, and against serotonin7 were used to immunostain colonies formed by co culturing ES cells EB5 with PA6 cells. Therein, it was confirmed that, not only neural cells which express neuronal marker NCAM, but also neural cells which express markers specific to various kinds of neurons were formed.

These arguments are not persuasive because in example 1 eight days after co culturing, EB5 with stromal cells the medium in the culturing vessel was removed and the cells were fixed

for 30 minutes by adding 4% p-formaldehyde solution [0451]. The fixed cells immunologic ally stained for the neural stem markers as shown in Table 1. However, the specification in example 1 fails to provide guidance then culturing continuously the cell in vitro in the absence of retinoic acid and in the presence of a stroma cell recognized by a monoclonal antibody produced by hybridoma FREM BP-7573 without forming embryoid body therefore, the an ordinary of skill in the art would have to perform undue experimentation to delineate the temporal culture conditions that would affect the differentiation of the ES cells into a neural crest cell or into a neural tube cell as instantly claimed.

Applicants argue in Example 14, antibodies against NCAM, against Pax-78, and against AP- 29 were used to immunostain colonies formed by co culturing ES cells EB5 with PA6 cells in the absence of retinoic acid. Therein, it was confirmed that, not only neural cells which express neuronal marker NCAM, but also neural cells which express neural tube dorsal side marker Pax-7 and neural crest cells marker AP-2 were formed.

In response, example 14 provides guidance for culture conditions as in example 1 and moreover regardless of the addition of shh or BMP4, most of the colonies formed as a result of co culturing of the ES cell EB5 with PA6 cell were stained with the anti-NCAM antibody similar to the results shown in Example 1, and 90% of the ES cell-derived colonies were positive in both cases [0538]. Therefore, for the same reasons as discussed above for example 1 the specification in example 14 fails to provide guidance then culturing continuously the cell in vitro in the absence of retinoic acid and in the presence of a stroma cell recognized by a monoclonal antibody produced by hybridoma FREM BP-7573 without forming embryoid body therefore, the an ordinary of skill in the art would have to perform undue experimentation to delineate the temporal culture conditions that would affect the differentiation of the ES cells into a neural crest cell or into a neural tube cell as instantly claimed.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 18, 20, 80-81are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over **Kuehn et al,** (Nature, 326: 295-298, 1987 (IDS).

Kuehn teaches co-culture of an embryonic stem cell in vitro in the absence of retinoic acid and in the presence of mitotically inactivated by mitomycin C treated 3T3 stromal cells for two days and then the stem cells expanded on STO feeder cells (p 297, 2nd column under Methods). The ES cells inherently differentiate into a neural crest cell or a neural tube cell as instantly claimed because the same culture method steps. Inherently, the stroma cell is recognized by the monoclonal antibody produced by the hybridoma FERM BP-7573 because there is in no structure of the stroma cells in the pending claims to differentiate them from those set forth by Kuehn. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO

can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima-facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531,173 USPQ 685 (1972).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571)272-3305. The examiner can normally be reached on Monday through Friday from 9 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paras Peter can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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